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(54) Title: TOPICAL ANTIGLAUCOMA COMPOSITIONS COMPRISING CARBONIC ANHYDRASE INHIBITORS AND BETA-BLOCKERS

(57) Abstract

Ophthalmic pharmaceutical compositions useful in controlling elevated intraocular pressure associated with glaucoma and ocular hypertension are described. The compositions comprise a combination of a beta-blocker and a carbonic anhydrase inhibitor to reduce the production of aqueous humor, preferably formulated as a suspension having a pH between about 6.8 and about 7.8. These compositions may additionally contain a mucomimetic anionic polymer and/or a finely-divided drug carrier substrate to provide sustained release. A method of controlling elevated intraocular pressure with these compositions is also described.

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TOPICAL ANTIGLAUCOMA COMPOSITIONS COMPRISING CARBONIC ANHYDRASE INHIBITORS AND BETA-BLOCKERS

This application is a continuation-in-part of U.S. Patent Application Serial No. 07/837,869, filed February 21, 1992.

Background of the Invention

The present invention relates to the field of ophthalmology. In particular, the invention relates to the treatment of glaucoma and associated elevations of intraocular pressure and to the treatment of ocular hypertension associated with other diseases or conditions.

Although the underlying causes of glaucoma are not understood, its symptoms often include elevated intraocular pressure, which may be caused either by over-production or inadequate outflow of aqueous humor. If left untreated, or if inadequately treated, glaucoma can lead to blindness or significant loss of vision. There is therefore a continuing need for therapies which control the elevated intraocular pressure associated with glaucoma.

There are currently a number of drugs utilized in the treatment of glaucoma, including: miotics (e.g., pilocarpine, carbachol and acetylcholinesterase inhibitors); sympathomimetics (e.g., epinephrine, dipivalylepinephrine and para-amino clonidine); beta-blockers (e.g., betaxolol, levobunolol and timolol); and carbonic anhydrase inhibitors (e.g., acetazolamide, methazolamide and ethoxzolamide). Miotics and sympathomimetics are believed to lower intraocular pressure ("IOP") by increasing the outflow of aqueous humor, while beta-blockers and carbonic anhydrase inhibitors are believed to lower IOP by decreasing the formation of aqueous humor. All four types of drugs have potentially serious side effects. Miotics such as pilocarpine can cause blurring of vision and other visual side effects, which may lead either to decreased patient compliance or to termination of therapy. Carbonic anhydrase inhibitors can also cause serious side effects which affect patient compliance and/or necessitate the withdrawal of treatment. Moreover, at least one beta-blocker, timolol, has

C_{1-6} alkyl or in which said carbon is substituted optionally with C_{1-6} alkyl, C_{1-6} alkoxy or OH; and when R_3 is in the 5 position and is H, Cl, Br, or C_{1-3} alkyl then neither R_1 nor R_2 can be H or C_{1-4} alkyl; and when G is C(=O) and in the 5- position and R_3 is H, then R_1 and R_2 cannot both be CH_3;

R_5 & R_6 are the same or different and are: H; C_{1-4} alkyl; C_{2-4} alkyl substituted optionally with OH, halogen, C_{1-4} alkoxy or C(=O)R_7; C_{1-4} alkoxy; C_{2-4} alkoxy substituted optionally with OH, halogen, C_{1-4} alkoxy or C(=O)R_7; C_{3-7} alkenyl unsubstituted or substituted optionally with OH, NR_5R_6, or C_{1-4} alkoxy; C_{3-7} alkynyl unsubstituted or substituted optionally with OH, NR_5R_6, or C_{1-4} alkoxy; C_{1-2}alkyl-C_{3-5}cycloalkyl; C(=O)R_7 or R_5 and R_6 can be joined to form a ring of 5 or 6 atoms selected from O, S, C or N, such as, pyrrolidine, oxazolidine, thiomorpholine, thiomorpholine 1,1 dioxide, morpholine, piperazine or thiazolidine 1,1-dioxide, which can be unsubstituted or substituted optionally on carbon with OH, (=O), halogen, C_{1-4} alkoxy, C(=O)R_7, C_{1-6} alkyl, C_{1-6} alkyl substituted optionally with OH, halogen, C_{1-4} alkoxy, C(=O)R_7 or on nitrogen with C_{1-4} alkoxy, C(=O)R_7, $S(=O)_mR_8$, C_{1-6} alkyl or C_{2-6} alkyl substituted optionally with OH, halogen, C_{1-4} alkoxy, C(=O)R_7 or on sulfur by $(=O)_m$, wherein m is 0 - 2;

R_7 is: C_{1-8} alkyl; C_{1-8} alkyl substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or C(=O)R_9; C_{1-4} alkoxy; C_{2-4} alkoxy substituted optionally with OH, NR_5R_6, halogen or C_{1-4} alkoxy; NR_5R_6; or phenyl or R_{10} either of which can be unsubstituted or substituted optionally with OH, halogen, C_{1-3} alkyl, C_{1-3} haloalkoxy, $(CH_2)_nNR_5R_6$, $S(=O)_mR_8$ or $SO_2NR_5R_6$, wherein n is 0 or 1 and m is 0-2;

R_8 is: C_{1-4} alkyl; C_{2-4} alkyl substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or C(=O)R_7;

R_9 is: C_{1-4} alkyl; C_{1-4} alkoxy; amino, C_{1-3} alkylamino, or di-C_{1-3} alkylamino;

R_{10} is: a monocyclic ring system of 5 or 6 atoms composed of C, N, O, and/or S, such as furan, thiophene, pyrrole, pyrazole, imidazole, triazole, tetrazole, oxazole, isoxazole, isothiazole, thiazole, thiadiazole, pyridine, pyrimidine, pyridazine, and pyrazine; and

G is: C(=O) or SO_2.

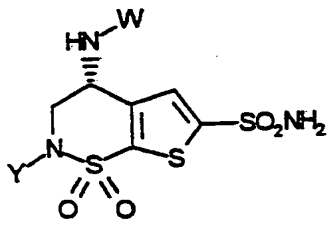
In the above definitions, the total number of carbon atoms in a substituent group is indicated by the C_{i-j} prefix where i and j are numbers from 1 to 8 for example. This C_{i-j} definition includes both the straight and branched chain isomers. For example, C_{1-4} alkyl would designate methyl through the butyl isomers; and C_{1-4} alkoxy would designate methoxy through the butoxy isomers.

The term "halogen," either alone or in compound words such as "haloalkyl," means fluorine, chlorine, bromine or iodine. Further, when used in compound words such as "haloalkyl," said alkyl may be partially or fully substituted with halogen atoms, which may be the same or different.

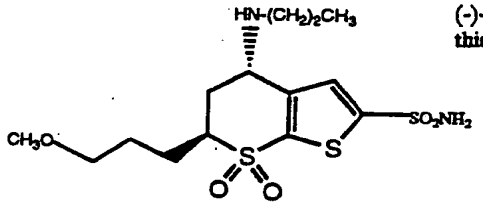
Structure (III) includes isomers, wherein R_3 and GNR_1R_2 are attached to the 4 and 5 position respectively or R_3 is attached to the 5 position and GNR_1R_2 is attached to the 4 position. Many of the novel compounds of Structure (III) possess one or more chiral centers and this invention includes all enantiomers, diastereomers and mixtures thereof.

Especially preferred CAIs of the present invention are those listed in Table 1, below.

TABLE 1



	W	Y	CHEMICAL NAME
1	CH_2CH_3	$(CH_2)_2OCH_2CH_3$	(R)-3,4-Dihydro-2-(2-ethoxy)ethyl-4-ethylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride
2	$(CH_2)_2CH_3$	$(CH_2)_2OCH_2CH_3$	(R)-3,4-Dihydro-2-(2-ethoxy)ethyl-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride
3	CH_2CH_3	$(CH_2)_3OCH_3$	(R)-3,4-Dihydro-4-ethylamino-2-(3-methoxy)propyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride
4	$(CH_2)_2CH_3$	$(CH_2)_3OCH_3$	(R)-3,4-Dihydro-2-(3-methoxy)propyl-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride
5	CH_2CH_3	$(CH_2)_2O(CH_2)_2OCH_3$	(R)-3,4-Dihydro-4-ethylamino-2-[2-methoxyethoxy)ethyl]-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride
6	$(CH_2)_2CH_3$	$(CH_2)_2O(CH_2)_2OCH_3$	(R)-3,4-Dihydro-2-[2-methoxyethoxy)ethyl]-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride
7	CH_2CH_3	$(CH_2)_3O(CH_2)_2OCH_3$	(R)-3,4-Dihydro-4-ethylamino-2-[3-(2-methoxy)ethoxy]propyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride
8	$(CH_2)_2CH_3$	$(CH_2)_3O(CH_2)_2OCH_3$	(R)-3,4-Dihydro-2-[3-(methoxyethoxy)propyl]-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride
9	CH_2CH_3	$(CH_2)_2OCH_3$	(R)-3,4-Dihydro-4-ethylamino-2-(2-methoxy)ethyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride
10	$(CH_2)_2CH_3$	$(CH_2)_2OCH_3$	(R)-3,4-Dihydro-2-(2-methoxy)ethyl-4-propylamino—2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride
11	CH_2CH_3	CH_3	(R)-3,4-Dihydro-4-ethylamino-2-methyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride
12	CH_2CH_3	$(CH_2)_4OCH_3$	(R)-4-ethylamino-3,4-dihydro-2-(4-methoxy)butyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide
13	$(CH_2)_2CH_3$	$(CH_2)_4OCH_3$	(R)-3,4-dihydro-2-(4-methoxy)butyl-4-propylamino-2-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide

14	CH_2CH_3	4-OCH_3-Ph	(R)-4-Ethylamino-2-(4-methoxyphenyl)-3,4-dihydro-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride
15	CH_2CH_3	3-OCH_3-Ph	(R)-4-Ethylamino-3,4-dihydro-2-(3-methoxyphenyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride
16	CH_2CH_3	4-OH-Ph	(R)-4-Ethylamino-2-(4-hydroxyphenyl)-3,4-dihydro-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride
17	CH_2CH_3	3-OH-Ph	(R)-4-Ethylamino-3,4-dihydro-2-(3-hydroxyphenyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride
18	CH_2CH_3	CH_2-(3-OH-Ph)	(R)-4-Ethylamino-3,4-dihydro-2-(3-hydroxyphenylmethyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride
19	CH_2CH_3	CH_2-(3-OCH_3-Ph)	(R)-4-Ethylamino-3,4-dihydro-2-(3-methoxyphenylmethyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride
20	CH_2CH_3	$CH_2CH(CH_3)_2$	(R)-4-Ethylamino-3,4-dihydro-2-(2-methylpropyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride
21	CH_2CH_3	$(CH_2)_6OH$	(R)-4-Ethylamino-3,4-dihydro-2-(6-hydroxyhexyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride
22	$CH_2CH(CH_3)_2$	$(CH_2)_3OH$	(R)-3,4-Dihydro-2-(3-hydroxypropyl)-4-(2-methylpropyl)amino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride hemihydrate
23			(-)-trans-5,6-dihydro-6-(3-methoxy)propyl-4-propylamino-4H-thieno-[2,3-b]thiopyran-2-sulfonamide 7,7-dioxide

In general, an amount of a beta-blocker less than or equal to about 2.0% by weight (wt%) and amount of a CAI less than or equal to about 5 wt% are used. It is preferred that an amount of beta-blocker between about 0.01 and about 1.0 wt% is used and it is especially preferred to use an amount between about 0.05 to about 0.5 wt%. An amount of a CAI between about 0.25 and about 3 wt% is preferred and an amount between about 0.5 and about 2 wt% is especially preferred. The ratio by weight of beta-blocker to CAI is generally between about 4:1 to about 1:300, preferably between about 1:1 to about 1:40.

The high molecular weight, anionic mucomimetic polymers useful in the present invention have a molecular weight between about 50,000 and 6 million daltons. The polymers are characterized as having carboxylic acid functional groups and preferably contain between 2 and 7 carbon atoms per functional group. The gels which form during preparation of the ophthalmic polymer dispersion have a viscosity between about 1,000 to about 300,000 centipoise (cps). Suitable polymers are carboxy vinyl polymers, preferably those called Carbomers, e.g., Carbopol® (B.F. Goodrich Co., Cleveland, Ohio). Specifically preferred are Carbopol® 934 and 940. Such polymers will typically be employed in an amount between about 0.05 and about 8.0 wt%, depending on the desired viscosity of the composition. Pourable liquid compositions generally comprise an amount of the polymer between about 0.05 and about 2.0 wt%.

The DCS component of the present compositions is added to provide an additional means of controlling release, as well as to prevent the stinging which often occurs with the topical administration of certain drugs, such as betaxolol. As used herein, the term "finely-divided drug carrier substrate" (or "DCS") means finely-divided solids, colloidal particles, or soluble polymers and/or polyelectrolytes which are capable of selective adsorption or binding with drug molecules. Examples of DCS include, but are not limited to: finely divided silica, such as fumed silica, silicates and bentonites; ion exchange resins, which can be anionic, cationic or non-ionic in nature; and soluble polymers, such as, alginic acid, pectin, soluble carrageenans, Carbopol®, and polystyrene sulfonic acid. Preferred DCS are the ion exchange resins. Some resins which are used in chromatography make ideal DCS for binding drugs in the compositions of the present invention. The DCS component is present in the compositions of the present invention at a concentration between about 0.05 and about 10.0% by weight.

The size of the DCS can be important, both with respect to mode of action and comfort. The average particle size of the typical commercially available form of the DCS material of choice, an ion exchange resin, is about 40 to about 150 microns. Such particles are most conveniently reduced to a particle size range of about 1.0 to

about 25.0 microns, preferably between about 1.0 and 10.0 microns, by ball milling, according to known techniques. In the alternative, small particles may be synthesized in the optimal size range of 3-7 microns. Although this procedure can be more expensive, it is superior in providing a more uniform and narrow distribution of sizes in the preferred range.

These anionic mucomimetic polymers and DCS are discussed in greater detail in U.S. 4,911,920 issued 27 March 1990 and EP 507 224 (published 7 October 1992). The entire contents of the patent and patent application are hereby incorporated by reference herein.

In addition to the above-described principal ingredients, the anti-glaucoma compositions of the present invention may further comprise various formulatory ingredients, such as antimicrobial preservatives and tonicity agents. Examples of suitable antimicrobial preservatives include: benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, Onamer M® and other agents equally well-known to those skilled in the art. Such preservatives, if utilized, will typically be employed in an amount between about 0.001 to 1.0 wt%. Examples of suitable agents which may be utilized to adjust the tonicity or osmolality of the formulations include: sodium chloride, potassium chloride, mannitol, dextrose, glycerin and propylene glycol. Such agents, if utilized, will typically be employed in an amount between about 0.1 to 10.0 wt%.

As will be appreciated by those skilled in the art, the compositions may be formulated in various dosage forms suitable for topical ophthalmic delivery, including solutions, suspensions, emulsions, gels and erodible solid ocular inserts. The compositions preferably are aqueous, have a pH between 5.0 to 7.8 and an osmolality between 280 to 320 milliOsmoles per kilogram (mOsm/kg).

The following example further illustrates the anti-glaucoma compositions of the present invention.

Example 1

The following formulations are typical of aqueous ophthalmic suspensions of the present invention.

INGREDIENT	AMOUNT (wt%)					
	A	B	C	D	E	F
Betaxolol HCl	0.28	—	0.28	—	0.28	—
Compound 3*	1.7**	1.7**	—	—	—	—
Compound 12*	—	—	1.5	1.5	—	—
Compound 13*	—	—	—	—	1.5	1.5
Timolol maleate	—	0.68	—	0.68	—	0.68
BAC	0.01	0.01	0.01	0.01	0.01	0.01
EDTA	0.05	0.05	0.05	0.05	0.05	0.05
Carbopol® 934P	0.4	0.4	0.4	0.4	0.4	0.4
Polysorbate 80	0.05	0.05	0.05	0.05	0.05	0.05
Mannitol	qs to 300 mOsm/kg	qs to 300 mOsm/kg	qs to 300 mOsm/kg	qs to 300 mOsm/kg	qs to 300 mOsm/kg	qs to 300 mOsm/kg
pH	qs to 7.5	qs to 7.5	qs to 7.5	qs to 7.5	qs to 7.5	qs to 7.5
Water	qs to 100	qs to 100	qs to 100	qs to 100	qs to 100	qs to 100

*See Table 1.
**Roughly equivalent to 1.5 wt% of the free base.

Preparation:

Compound 3, 12 or 13, and betaxolol or timolol are mixed in 50% of the total water volume component to form an uniform dispersion. Carbopol 934P is slowly added as an aqueous dispersion. The mixture is then homogenized at high speed. The other ingredients are added as aqueous solutions and then water is added to make the final volume. The resultant products, A-F, will be white uniform suspensions.

Example 2

The following formulations are typical of aqueous ophthalmic suspensions of the present invention.

INGREDIENT	AMOUNT (wt%)							
	G	H	J	K	L	M	N	O
Betaxolol HCl	0.28	0.56	0.28	0.56	0.28	0.56	0.28	0.56
Compound 3*	—	—	1.7**	1.7**	—	—	—	—
Compound 9*	1.67**	1.67**	—	—	1.67**	1.67**	1.67**	1.67**
Compound 12*	—	—	—	—	1.5	1.5	—	—
Compound 13*	—	—	—	—	—	—	1.5	1.5
BAC	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
EDTA	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Amberlite® IRP-69	0.25	0.50	0.25	0.50	0.25	0.50	0.25	0.50
Carbopol® 934P	0.4	2.0	0.4	2.0	0.4	2.0	0.4	2.0
Polysorbate 80	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Mannitol	qs to 300 mOsm/kg	qs to 300 mOsm/kg	qs to 300 mOsm/kg	qs to 300 mOsm/kg	qs to 300 mOsm/kg	qs to 300 mOsm/kg	qs to 300 mOsm/kg	qs to 300 mOsm/kg
pH	qs to 7.5	qs to 7.5	qs to 7.5	qs to 7.5	qs to 7.5	qs to 7.5	qs to 7.5	qs to 7.5
Water	qs to 100	qs to 100	qs to 100	qs to 100	qs to 100	qs to 100	qs to 100	qs to 100

*See Table 1.
**Roughly equivalent to 1.5 wt% of the free base.

Preparation:

Amberlite, betaxolol and Compound 3, 9, 12 or 13 are mixed in 50% of the total water volume component to form an uniform dispersion. Carbopol 934P is slowly added as an aqueous dispersion. The mixture is then homogenized at high speed. The other ingredients are added as aqueous solutions and then water is added to make the final volume. The resultant products, G-O, will be white uniform suspensions.

The present invention is also directed to methods of treating and controlling ocular hypertension associated with glaucoma and other ophthalmic diseases and abnormalities. The methods comprise topically applying to the affected eye(s) of the

patient a therapeutically effective amount of a composition according to the present invention. The frequency and amount of dosage will be determined by the clinician based on various clinical factors. The methods will typically comprise topical application of one or two drops (or an equivalent amount of a solid or semi-solid dosage form) to the affected eye one to two times per day.

The invention has been described by reference to certain preferred embodiments; however, it should be understood that it may be embodied in other specific forms or variations thereof without departing from its spirit or essential characteristics. The embodiments described above are therefore considered to be illustrative in all respects and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description.

What is Claimed is:

1. A topical ophthalmic composition for the treatment of glaucoma and ocular hypertension, comprising a beta-blocker and a carbonic anhydrase inhibitor in an ophthalmically acceptable vehicle.

2. The composition of claim 1, wherein the composition is a suspension and the final composition pH is between about 5.0 and about 7.8.

3. The composition of claim 2, wherein the final composition concentration of beta-blocker is less than or equal to about 2.0 wt%, and the final composition concentration of carbonic anhydrase inhibitor is less than or equal to about 5 wt%.

4. The composition of claim 3, wherein the final composition concentration of the beta-blocker is between about 0.1 and about 1.0 wt%.

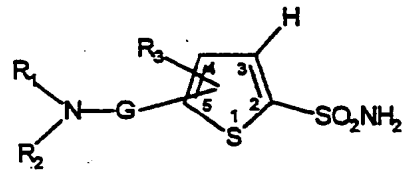
5. The composition of claim 4, wherein the final composition concentration of the beta-blocker is between about 0.25 and about 0.5 wt%.

6. The composition of claim 5, wherein the final composition concentration of the beta-blocker is 0.25 wt%.

7. The composition of claim 3, wherein the final composition concentration of the carbonic anhydrase inhibitor is between about 0.25 and about 3 wt%.

8. The composition of claim 7, wherein the final composition concentration of the carbonic anhydrase inhibitor is about 1.5 wt%.

9. The composition of claim 2, wherein the carbonic anhydrase inhibitor has the formula:



(III)

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is: H; C_{1-4} alkyl; C_{2-4} alkyl substituted optionally with OH, halogen, C_{1-4} alkoxy or $C(=O)R_7$;

R_2 is: H; C_{1-8} alkyl; C_{2-8} alkyl substituted with OH, NR_5R_6, halogen, C_{1-4} alkoxy, C_{2-4}alkoxyC_{1-4}alkoxy, $OC(=O)R_7$, or $C(=O)R_7$; C_{3-7} alkenyl unsubstituted or substituted optionally with OH, NR_5R_6, or C_{1-4} alkoxy; C_{3-7} alkynyl unsubstituted or substituted optionally with OH, NR_5R_6, or C_{1-4} alkoxy; C_{1-3} alkyl substituted with phenyl or R_{10} either of which can be unsubstituted or substituted optionally with C_{1-3} alkyl, C_{1-3} haloalkyl, OH, $(CH_2)_nNR_5R_6$, halogen, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $C(=O)R_7$, $S(=O)_mR_8$ or $SO_2NR_5R_6$, wherein m is 0 - 2 and n is 0 - 2; C_{2-4} alkoxy substituted optionally with NR_5R_6, halogen, C_{1-4} alkoxy, or $C(=O)R_7$; phenyl or R_{10} either of which can be unsubstituted or substituted optionally with C_{1-3} alkyl, C_{1-3} haloalkyl, OH, $(CH_2)_nNR_5R_6$, halogen, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $C(=O)R_7$, $S(=O)_mR_8$ or $SO_2NR_5R_6$, wherein m is 0 - 2 and n is 0 - 2; provided that R_1 and R_2 cannot both be H; or R_1 and R_2 can be joined to form a saturated ring of 5 or 6 atoms selected from O, S, C or N, such as, pyrrolidine, oxazolidine, thiomorpholine, thiomorpholine 1,1 dioxide, morpholine, piperazine, thiazolidine 1,1 dioxide, or tetrahydrooxazine, which can be unsubstituted or substituted optionally on carbon with OH, NR_5R_6, halogen, C_{1-4} alkoxy, $C(=O)R_7$, C_{1-6} alkyl, C_{1-6} alkyl substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy, $C(=O)R_7$ or on nitrogen with NR_5R_6, C_{1-4} alkoxy, $C(=O)R_7$, C_{1-6} alkyl or C_{2-6} alkyl substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or $C(=O)R_7$;

R_3 is: H; halogen; C_{1-4} alkyl; C_{1-8} alkoxy; C_{1-8} alkylthiol; C_{2-8} alkoxy substituted

optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or $C(=O)R_7$; C_{1-4} alkyl substituted optionally with R_4; or R_1 and R_3 can be joined together with carbon atoms to form a ring of from 5 to 7 members in which said carbon atoms can be unsubstituted or substituted optionally with R_4;

R_4 is: OH; C_{1-4} alkyl unsubstituted or substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or $C(=O)R_7$; C_{1-4} alkoxy; C_{2-4} alkoxy substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or $C(=O)R_7$; NR_5R_6; phenyl or R_{10} either of which can be unsubstituted or substituted optionally with OH, $(CH_2)_nNR_5R_6$, halogen, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $C(=O)R_7$, $S(=O)_mR_8$ or $SO_2NR_5R_6$, wherein m is 0 - 2 and n is 0 - 2;

Provided that when G is SO_2 and R_3 is in the 4 position and is H or halogen then R_1 and R_2 are not H, C_{1-6} alkyl substituted optionally with OH, C_{1-6} alkoxy, C_{2-6} alkoxycarbonyl, C_{2-6} alkenyl, phenyl, phenoxy, pyridyl, tetrahydrofuryl, C_{2-6} alkanoyl, C_{2-6} alkenyl, nor are they joined to form a 5, 6 or 7 member ring, saturated or unsaturated, comprised of atoms selected optionally from C, O, S, N in which said nitrogen, when saturated, is substituted optionally with H or C_{1-6} alkyl or in which said carbon is substituted optionally with C_{1-6} alkyl, C_{1-6} alkoxy or OH; and when R_3 is in the 5 position and is H, Cl, Br, or C_{1-3} alkyl then neither R_1 nor R_2 can be H or C_{1-4} alkyl; and when G is $C(=O)$ and in the 5- position and R_3 is H, then R_1 and R_2 cannot both be CH_3;

R_5 & R_6 are the same or different and are: H; C_{1-4} alkyl; C_{2-4} alkyl substituted optionally with OH, halogen, C_{1-4} alkoxy or $C(=O)R_7$; C_{1-4} alkoxy; C_{2-4} alkoxy substituted optionally with OH, halogen, C_{1-4} alkoxy or $C(=O)R_7$; C_{3-7} alkenyl unsubstituted or substituted optionally with OH, NR_5R_6, or C_{1-4} alkoxy; C_{3-7} alkynyl unsubstituted or substituted optionally with OH, NR_5R_6, or C_{1-4} alkoxy; C_{1-2}alkyl-C_{3-5}cycloalkyl; $C(=O)R_7$ or R_5 and R_6 can be joined to form a ring of 5 or 6 atoms selected from O, S, C or N, such as, pyrrolidine, oxazolidine, thiomorpholine, thiomorpholine 1,1 dioxide, morpholine, piperazine or thiazolidine 1,1-dioxide, which can be unsubstituted or substituted optionally on carbon with OH, (=O), halogen, C_{1-4} alkoxy, $C(=O)R_7$, C_{1-6} alkyl, C_{1-6} alkyl substituted optionally with OH, halogen, C_{1-4} alkoxy, $C(=O)R_7$ or on nitrogen with C_{1-4} alkoxy, $C(=O)R_7$, $S(=O)_mR_8$, C_{1-6} alkyl or C_{2-6} alkyl substituted

optionally with OH, halogen, C_{1-4} alkoxy, $C(=O)R_7$ or on sulfur by $(=O)_m$, wherein m is 0 - 2;

R_7 is: C_{1-8} alkyl; C_{1-8} alkyl substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or $C(=O)R_9$; C_{1-4} alkoxy; C_{2-4} alkoxy substituted optionally with OH, NR_5R_6, halogen or C_{1-4} alkoxy; NR_5R_6; or phenyl or R_{10} either of which can be unsubstituted or substituted optionally with OH, halogen, C_{1-3} alkyl, C_{1-3} haloalkoxy, $(CH_2)_nNR_5R_6$, $S(=O)_mR_8$ or $SO_2NR_5R_6$, wherein n is 0 or 1 and m is 0-2;

R_8 is: C_{1-4} alkyl; C_{2-4} alkyl substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or $C(=O)R_7$;

R_9 is: C_{1-4} alkyl; C_{1-4} alkoxy; amino, C_{1-3} alkylamino, or di-C_{1-3} alkylamino;

R_{10} is: a monocyclic ring system of 5 or 6 atoms composed of C, N, O, and/or S, such as furan, thiophene, pyrrole, pyrazole, imidazole, triazole, tetrazole, oxazole, isoxazole, isothiazole, thiazole, thiadiazole, pyridine, pyrimidine, pyridazine, and pyrazine; and

G is: $C(=O)$ or SO_2.

10. The composition of claim 9, wherein the carbonic anhydrase inhibitor is selected from the group consisting of: (R)-3,4-Dihydro-2-(2-ethoxy)ethyl-4-ethylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-3,4-Dihydro-2-(2-ethoxy)ethyl-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-3,4-Dihydro-4-ethylamino-2-(3-methoxy)propyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-3,4-Dihydro-2-(3-methoxy)propyl-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-3,4-Dihydro-4-ethylamino-2-[2-methoxyethoxy)ethyl]-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-3,4-Dihydro-2-[2-methoxyethoxy)ethyl]-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-3,4-Dihydro-4-ethylamino-2-[3-(2-methoxy)ethoxy]propyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-3,4-Dihydro-2-[3-(methoxyethoxy)propyl]-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-3,4-Dihydro-4-ethylamino-2-(2-methoxy)ethyl-2H-thieno[3,2-e]-1,2-thiazine-6-

sulfonamide 1,1-dioxide hydrochloride; (R)-3,4-Dihydro-2-(2-methoxy)ethyl-4-propylamino--2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-3,4-Dihydro-4-ethylamino-2-methyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-4-ethylamino-3,4-dihydro-2-(4-methoxy)butyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide; (R)-3,4-dihydro-2-(4-methoxy)butyl-4-propylamino-2-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide; (R)-4-Ethylamino-2-(4-methoxyphenyl)-3,4-dihydro-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-4-Ethylamino-3,4-dihydro-2-(3-methoxyphenyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-4-Ethylamino-2-(4-hydroxyphenyl)-3,4-dihydro-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-4-Ethylamino-3,4-dihydro-2-(3-hydroxyphenyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-4-Ethylamino-3,4-dihydro-2-(3-hydroxyphenylmethyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-4-Ethylamino-3,4-dihydro-2-(3-methoxyphenylmethyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-4-Ethylamino-3,4-dihydro-2-(2-methylpropyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-4-Ethylamino-3,4-dihydro-2-(6-hydroxyhexyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-3,4-Dihydro-2-(3-hydroxypropyl)-4-(2-methylpropyl)amino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride hemihydrate; and (-)-trans-5,6-dihydro-6-(3-methoxy)propyl-4-propylamino-4H-thieno-[2,3-b]thiopyran-2-sulfonamide 7,7-dioxide.

11. The composition of claim 10, wherein the carbonic anhydrase inhibitor is selected from the group consisting of: (R)-3,4-Dihydro-4-ethylamino-2-(3-methoxy)propyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride and (R)-3,4-Dihydro-4-ethylamino-2-(2-methoxy)ethyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-4-ethylamino-3,4-dihydro-2-(4-methoxy)butyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide; (R)-3,4-dihydro-2-(4-methoxy)butyl-4-propylamino-2-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide; (-)-trans-5,6-dihydro-6-(3-methoxy)propyl-4-propylamino-4H-thieno-[2,3-b]thiopyran-2-sulfonamide 7,7-dioxide.

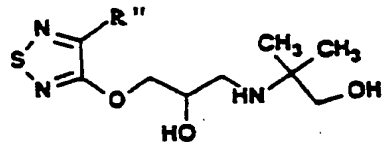
12. The composition of claim 2, wherein the beta-blocker is selected from the racemic and enantiomeric forms of: betaxolol, timolol, metoprolol, befunolol, falintolol, levobunolol, carteolol, mepindolol, pindolol, bisoprolol, bopindolol, atenolol, arotinolol, acebutolol, nadolol, celiprolol, metipranolol, bevantolol, ICI 118,551, pamatolol, penbutolol, toliprolol, tiprenolol, practolol, procinolol, exaprolol, cicloprolol, carazolol, tazolol, tienoxolol, oxprenolol, propranolol, IPS 339, labetolol, dilevalol, esmolol, bupranolol, bunolol, isoxaprolol, diacetolol, hydroxylevobunolol, carvedilol, and their pharmaceutically acceptable salts.

13. The composition of claim 12, wherein the beta-blocker is selected from the racemic and enantiomeric forms of: betaxolol, timolol, carteolol, levobunolol and hydroxylevobunolol, and their pharmaceutically acceptable salts.

14. The composition of claim 13, wherein the beta-blocker is betaxolol or a pharmaceutically acceptable salt thereof.

15. The composition of claim 13, wherein the beta-blocker is S-timolol or a pharmaceutically acceptable salt thereof.

16. The composition of claim 2, wherein the beta-blocker is a thiadiazole of formula:



(II)

and optically active isomers and pharmacologically acceptable salts thereof, wherein R" is selected from the group consisting of: hydrogen, halogen, C_{1-5} alkyl, C_{2-5} mono-alkenyl, C_{2-5} alkoxy, C_{3-6} cycloalkyl, phenyl, phenalkyl, morpholino, furyl, thienyl and pyrryl.

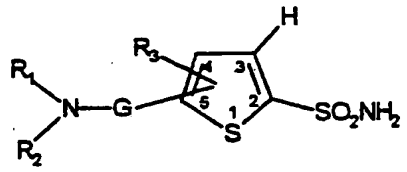
17. The composition of claim 16, wherein R" is selected from the group consisting of: chlorine, ethyl, allyl, cyclopropyl, ethoxy, phenyl, phenyl-chloromethyl and 2-(cyclopropylmethoxy)ethyl.

18. The composition of claim 1, further comprising an anionic mucomimetic polymer wherein the final composition concentration of the anionic mucomimetic polymer is between about 0.05 and about 8.0 wt%.

19. The composition of claim 18, wherein the final composition concentration of beta-blocker is less than or equal to about 2.0 wt%, and the final composition concentration of carbonic anhydrase inhibitor is less than or equal to about 5 wt%

20. The composition of claim 19, further comprising a finely-divided drug carrier substrate, wherein the final composition concentration of the finely-divided drug carrier substrate is between about 0.05 and about 10.0 wt%.

21. The composition of claim 18, wherein the carbonic anhydrase inhibitor has the formula:



(III)

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is: H; C_{1-4} alkyl; C_{2-4} alkyl substituted optionally with OH, halogen, C_{1-4} alkoxy or $C(=O)R_7$;

R_2 is: H; C_{1-8} alkyl; C_{2-8} alkyl substituted with OH, NR_5R_6, halogen, C_{1-4} alkoxy, C_{2-4}alkoxyC_{1-4}alkoxy, $OC(=O)R_7$, or $C(=O)R_7$; C_{3-7} alkenyl unsubstituted or substituted optionally with OH, NR_5R_6, or C_{1-4} alkoxy; C_{3-7} alkynyl unsubstituted or substituted optionally with OH, NR_5R_6, or C_{1-4} alkoxy; C_{1-3} alkyl substituted with phenyl or R_{10} either of which can be unsubstituted or

substituted optionally with C_{1-3} alkyl, C_{1-3} haloalkyl, OH, $(CH_2)_nNR_5R_6$, halogen, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $C(=O)R_7$, $S(=O)_mR_8$ or $SO_2NR_5R_6$, wherein m is 0 - 2 and n is 0 - 2; C_{2-4} alkoxy substituted optionally with NR_5R_6, halogen, C_{1-4} alkoxy, or $C(=O)R_7$; phenyl or R_{10} either of which can be unsubstituted or substituted optionally with C_{1-3} alkyl, C_{1-3} haloalkyl, OH, $(CH_2)_nNR_5R_6$, halogen, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $C(=O)R_7$, $S(=O)_mR_8$ or $SO_2NR_5R_6$, wherein m is 0 - 2 and n is 0 - 2; provided that R_1 and R_2 cannot both be H; or R_1 and R_2 can be joined to form a saturated ring of 5 or 6 atoms selected from O, S, C or N, such as, pyrrolidine, oxazolidine, thiomorpholine, thiomorpholine 1,1 dioxide, morpholine, piperazine, thiazolidine 1,1 dioxide, or tetrahydrooxazine, which can be unsubstituted or substituted optionally on carbon with OH, NR_5R_6, halogen, C_{1-4} alkoxy, $C(=O)R_7$, C_{1-6} alkyl, C_{1-6} alkyl substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy, $C(=O)R_7$ or on nitrogen with NR_5R_6, C_{1-4} alkoxy, $C(=O)R_7$, C_{1-6} alkyl or C_{2-6} alkyl substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or $C(=O)R_7$;

R_3 is: H; halogen; C_{1-4} alkyl; C_{1-8} alkoxy; C_{1-8} alkylthiol; C_{2-8} alkoxy substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or $C(=O)R_7$; C_{1-4} alkyl substituted optionally with R_4; or R_1 and R_3 can be joined together with carbon atoms to form a ring of from 5 to 7 members in which said carbon atoms can be unsubstituted or substituted optionally with R_4;

R_4 is: OH; C_{1-4} alkyl unsubstituted or substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or $C(=O)R_7$; C_{1-4} alkoxy; C_{2-4} alkoxy substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or $C(=O)R_7$; NR_5R_6; phenyl or R_{10} either of which can be unsubstituted or substituted optionally with OH, $(CH_2)_nNR_5R_6$, halogen, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $C(=O)R_7$, $S(=O)_mR_8$ or $SO_2NR_5R_6$, wherein m is 0 - 2 and n is 0 - 2;

Provided that when G is SO_2 and R_3 is in the 4 position and is H or halogen then R_1 and R_2 are not H, C_{1-6} alkyl substituted optionally with OH, C_{1-6} alkoxy, C_{2-6} alkoxycarbonyl, C_{2-6} alkenyl, phenyl, phenoxy, pyridyl, tetrahydrofuryl, C_{2-6} alkanoyl, C_{2-6} alkenyl, nor are they joined to form a 5, 6 or 7 member ring, saturated or unsaturated, comprised of atoms selected optionally from C, O, S,

N in which said nitrogen, when saturated, is substituted optionally with H or C_{1-6} alkyl or in which said carbon is substituted optionally with C_{1-6} alkyl, C_{1-6} alkoxy or OH; and when R_3 is in the 5 position and is H, Cl, Br, or C_{1-3} alkyl then neither R_1 nor R_2 can be H or C_{1-4} alkyl; and when G is C(=O) and in the 5- position and R_3 is H, then R_1 and R_2 cannot both be CH_3;

R_5 & R_6 are the same or different and are: H; C_{1-4} alkyl; C_{2-4} alkyl substituted optionally with OH, halogen, C_{1-4} alkoxy or $C(=O)R_7$; C_{1-4} alkoxy; C_{2-4} alkoxy substituted optionally with OH, halogen, C_{1-4} alkoxy or $C(=O)R_7$; C_{3-7} alkenyl unsubstituted or substituted optionally with OH, NR_5R_6, or C_{1-4} alkoxy; C_{3-7} alkynyl unsubstituted or substituted optionally with OH, NR_5R_6, or C_{1-4} alkoxy; C_{1-2}alkyl-C_{3-5}cycloalkyl; $C(=O)R_7$ or R_5 and R_6 can be joined to form a ring of 5 or 6 atoms selected from O, S, C or N, such as, pyrrolidine, oxazolidine, thiomorpholine, thiomorpholine 1,1 dioxide, morpholine, piperazine or thiazolidine 1,1-dioxide, which can be unsubstituted or substituted optionally on carbon with OH, (=O), halogen, C_{1-4} alkoxy, $C(=O)R_7$, C_{1-6} alkyl, C_{1-6} alkyl substituted optionally with OH, halogen, C_{1-4} alkoxy, $C(=O)R_7$ or on nitrogen with C_{1-4} alkoxy, $C(=O)R_7$, $S(=O)_mR_8$, C_{1-6} alkyl or C_{2-6} alkyl substituted optionally with OH, halogen, C_{1-4} alkoxy, $C(=O)R_7$ or on sulfur by $(=O)_m$, wherein m is 0 - 2;

R_7 is: C_{1-8} alkyl; C_{1-8} alkyl substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or $C(=O)R_9$; C_{1-4} alkoxy; C_{2-4} alkoxy substituted optionally with OH, NR_5R_6, halogen or C_{1-4} alkoxy; NR_5R_6; or phenyl or R_{10} either of which can be unsubstituted or substituted optionally with OH, halogen, C_{1-3} alkyl, C_{1-3} haloalkoxy, $(CH_2)_nNR_5R_6$, $S(=O)_mR_8$ or $SO_2NR_5R_6$, wherein n is 0 or 1 and m is 0-2;

R_8 is: C_{1-4} alkyl; C_{2-4} alkyl substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or $C(=O)R_7$;

R_9 is: C_{1-4} alkyl; C_{1-4} alkoxy; amino, C_{1-3} alkylamino, or di-C_{1-3} alkylamino;

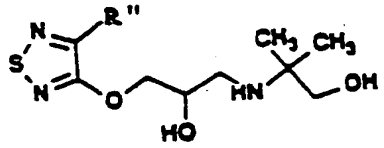
R_{10} is: a monocyclic ring system of 5 or 6 atoms composed of C, N, O, and/or S, such as furan, thiophene, pyrrole, pyrazole, imidazole, triazole, tetrazole, oxazole,

isoxazole, isothiazole, thiazole, thiadiazole, pyridine, pyrimidine, pyridazine, and pyrazine; and

G is: C(=O) or SO_2.

22. The composition of claim 18, wherein the beta-blocker is selected from the racemic and enantiomeric forms of: betaxolol, timolol, metoprolol, befunolol, falintolol, levobunolol, carteolol, mepindolol, pindolol, bisoprolol, bopindolol, atenolol, arotinolol, acebutolol, nadolol, celiprolol, metipranolol, bevantolol, ICI 118,551, pamatolol, penbutolol, toliprolol, tiprenolol, practolol, procinolol, exaprolol, cicloprolol, carazolol, tazolol, tienoxolol, oxprenolol, propranolol, IPS 339, labetolol, dilevalol, esmolol, bupranolol, bunolol, isoxaprolol, diacetolol, hydroxylevobunolol, carvedilol, and their pharmaceutically acceptable salts.

23. The composition of claim 18, wherein the beta-blocker is a thiadiazole of formula:



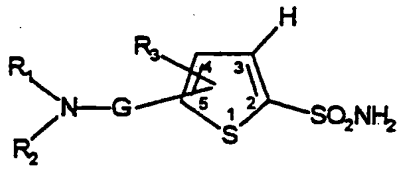
(II)

and optically active isomers and pharmacologically acceptable salts thereof, wherein R" is selected from the group consisting of: hydrogen, halogen, C_{1-5} alkyl, C_{2-5} mono-alkenyl, C_{2-5} alkoxy, C_{3-6} cycloalkyl, phenyl, phenalkyl, morpholino, furyl, thienyl and pyrryl.

24. A method for the treatment of glaucoma and ocular hypertension, comprising applying to an affected eye a composition comprising a beta-blocker and a carbonic anhydrase inhibitor in an ophthalmically acceptable vehicle.

25. The method of claim 24, wherein: the final composition concentration of the beta-blocker is less than or equal to about 2.0 wt%, and the final composition concentration of the carbonic anhydrase inhibitor is less than or equal to about 5 wt%.

26. The method of claim 24, wherein the carbonic anhydrase inhibitor has the formula:



(III)

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is: H; C_{1-4} alkyl; C_{2-4} alkyl substituted optionally with OH, halogen, C_{1-4} alkoxy or $C(=O)R_7$;

R_2 is: H; C_{1-8} alkyl; C_{2-8} alkyl substituted with OH, NR_5R_6, halogen, C_{1-4} alkoxy, C_{2-4}alkoxyC_{1-4}alkoxy, $OC(=O)R_7$, or $C(=O)R_7$; C_{3-7} alkenyl unsubstituted or substituted optionally with OH, NR_5R_6, or C_{1-4} alkoxy; C_{3-7} alkynyl unsubstituted or substituted optionally with OH, NR_5R_6, or C_{1-4} alkoxy; C_{1-3} alkyl substituted with phenyl or R_{10} either of which can be unsubstituted or substituted optionally with C_{1-3} alkyl, C_{1-3} haloalkyl, OH, $(CH_2)_nNR_5R_6$, halogen, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $C(=O)R_7$, $S(=O)_mR_8$ or $SO_2NR_5R_6$, wherein m is 0 - 2 and n is 0 - 2; C_{2-4} alkoxy substituted optionally with NR_5R_6, halogen, C_{1-4} alkoxy, or $C(=O)R_7$; phenyl or R_{10} either of which can be unsubstituted or substituted optionally with C_{1-3} alkyl, C_{1-3} haloalkyl, OH, $(CH_2)_nNR_5R_6$, halogen, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $C(=O)R_7$, $S(=O)_mR_8$ or $SO_2NR_5R_6$, wherein m is 0 - 2 and n is 0 - 2; provided that R_1 and R_2 cannot both be H; or R_1 and R_2 can be joined to form a saturated ring of 5 or 6 atoms selected from O, S, C or N, such as, pyrrolidine, oxazolidine, thiomorpholine, thiomorpholine 1,1 dioxide, morpholine, piperazine, thiazolidine 1,1 dioxide, or tetrahydrooxazine, which can be unsubstituted or substituted optionally on carbon with OH, NR_5R_6, halogen, C_{1-4} alkoxy, $C(=O)R_7$, C_{1-6} alkyl, C_{1-6} alkyl substituted optionally with OH, NR_5R_6, halogen,

C_{1-4} alkoxy, $C(=O)R_7$ or on nitrogen with NR_5R_6, C_{1-4} alkoxy, $C(=O)R_7$, C_{1-6} alkyl or C_{2-6} alkyl substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or $C(=O)R_7$;

R_3 is: H; halogen; C_{1-4} alkyl; C_{1-8} alkoxy; C_{1-8} alkylthiol; C_{2-8} alkoxy substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or $C(=O)R_7$; C_{1-4} alkyl substituted optionally with R_4; or R_1 and R_3 can be joined together with carbon atoms to form a ring of from 5 to 7 members in which said carbon atoms can be unsubstituted or substituted optionally with R_4;

R_4 is: OH; C_{1-4} alkyl unsubstituted or substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or $C(=O)R_7$; C_{1-4} alkoxy; C_{2-4} alkoxy substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or $C(=O)R_7$; NR_5R_6; phenyl or R_{10} either of which can be unsubstituted or substituted optionally with OH, $(CH_2)_nNR_5R_6$, halogen, C_{1-4} alkoxy, C_{1-4} haloalkoxy, $C(=O)R_7$, $S(=O)_mR_8$ or $SO_2NR_5R_6$, wherein m is 0 - 2 and n is 0 - 2;

Provided that when G is SO_2 and R_3 is in the 4 position and is H or halogen then R_1 and R_2 are not H, C_{1-6} alkyl substituted optionally with OH, C_{1-6} alkoxy, C_{2-6} alkoxycarbonyl, C_{2-6} alkenyl, phenyl, phenoxy, pyridyl, tetrahydrofuryl, C_{2-6} alkanoyl, C_{2-6} alkenyl, nor are they joined to form a 5, 6 or 7 member ring, saturated or unsaturated, comprised of atoms selected optionally from C, O, S, N in which said nitrogen, when saturated, is substituted optionally with H or C_{1-6} alkyl or in which said carbon is substituted optionally with C_{1-6} alkyl, C_{1-6} alkoxy or OH; and when R_3 is in the 5 position and is H, Cl, Br, or C_{1-3} alkyl then neither R_1 nor R_2 can be H or C_{1-4} alkyl; and when G is C(=O) and in the 5- position and R_3 is H, then R_1 and R_2 cannot both be CH_3;

R_5 & R_6 are the same or different and are: H; C_{1-4} alkyl; C_{2-4} alkyl substituted optionally with OH, halogen, C_{1-4} alkoxy or $C(=O)R_7$; C_{1-4} alkoxy; C_{2-4} alkoxy substituted optionally with OH, halogen, C_{1-4} alkoxy or $C(=O)R_7$; C_{3-7} alkenyl unsubstituted or substituted optionally with OH, NR_5R_6, or C_{1-4} alkoxy; C_{3-7} alkynyl unsubstituted or substituted optionally with OH, NR_5R_6, or C_{1-4} alkoxy; C_{1-2}alkyl-C_{3-5}cycloalkyl; $C(=O)R_7$ or R_5 and R_6 can be joined to form a ring of 5 or 6 atoms selected from O, S, C or N, such as, pyrrolidine, oxazolidine, thiomorpholine, thiomorpholine 1,1 dioxide, morpholine, piperazine or

thiazolidine 1,1-dioxide, which can be unsubstituted or substituted optionally on carbon with OH, (=O), halogen, C_{1-4} alkoxy, $C(=O)R_7$, C_{1-6} alkyl, C_{1-6} alkyl substituted optionally with OH, halogen, C_{1-4} alkoxy, $C(=O)R_7$ or on nitrogen with C_{1-4} alkoxy, $C(=O)R_7$, $S(=O)_mR_8$, C_{1-6} alkyl or C_{2-6} alkyl substituted optionally with OH, halogen, C_{1-4} alkoxy, $C(=O)R_7$ or on sulfur by $(=O)_m$, wherein m is 0 - 2;

R_7 is: C_{1-8} alkyl; C_{1-8} alkyl substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or $C(=O)R_9$; C_{1-4} alkoxy; C_{2-4} alkoxy substituted optionally with OH, NR_5R_6, halogen or C_{1-4} alkoxy; NR_5R_6; or phenyl or R_{10} either of which can be unsubstituted or substituted optionally with OH, halogen, C_{1-3} alkyl, C_{1-3} haloalkoxy, $(CH_2)_nNR_5R_6$, $S(=O)_mR_8$ or $SO_2NR_5R_6$, wherein n is 0 or 1 and m is 0-2;

R_8 is: C_{1-4} alkyl; C_{2-4} alkyl substituted optionally with OH, NR_5R_6, halogen, C_{1-4} alkoxy or $C(=O)R_7$;

R_9 is: C_{1-4} alkyl; C_{1-4} alkoxy; amino, C_{1-3} alkylamino, or di-C_{1-3} alkylamino;

R_{10} is: a monocyclic ring system of 5 or 6 atoms composed of C, N, O, and/or S, such as furan, thiophene, pyrrole, pyrazole, imidazole, triazole, tetrazole, oxazole, isoxazole, isothiazole, thiazole, thiadiazole, pyridine, pyrimidine, pyridazine, and pyrazine; and

G is: $C(=O)$ or SO_2.

27. The method of claim 26, wherein the carbonic anhydrase inhibitor is selected from the group consisting of: (R)-3,4-Dihydro-2-(2-ethoxy)ethyl-4-ethylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-3,4-Dihydro-2-(2-ethoxy)ethyl-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-3,4-Dihydro-4-ethylamino-2-(3-methoxy)propyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-3,4-Dihydro-2-(3-methoxy)propyl-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-3,4-Dihydro-4-ethylamino-2-[2-methoxyethoxy)ethyl]-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-3,4-Dihydro-2-[2-methoxyethoxy)ethyl]-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-3,4-Dihydro-4-ethylamino-2-[3-(2-methoxy)ethoxy]propyl-

2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-3,4-Dihydro-2-[3-(methoxyethoxy)propyl]-4-propylamino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-3,4-Dihydro-4-ethylamino-2-(2-methoxy)ethyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-3,4-Dihydro-2-(2-methoxy)ethyl-4-propylamino--2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-3,4-Dihydro-4-ethylamino-2-methyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-4-ethylamino-3,4-dihydro-2-(4-methoxy)butyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide; (R)-3,4-dihydro-2-(4-methoxy)butyl-4-propylamino-2-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide; (R)-4-Ethylamino-2-(4-methoxyphenyl)-3,4-dihydro-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-4-Ethylamino-3,4-dihydro-2-(3-methoxyphenyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-4-Ethylamino-2-(4-hydroxyphenyl)-3,4-dihydro-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-4-Ethylamino-3,4-dihydro-2-(3-hydroxyphenyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-4-Ethylamino-3,4-dihydro-2-(3-hydroxyphenylmethyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-4-Ethylamino-3,4-dihydro-2-(3-methoxyphenylmethyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-4-Ethylamino-3,4-dihydro-2-(2-methylpropyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-4-Ethylamino-3,4-dihydro-2-(6-hydroxyhexyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-3,4-Dihydro-2-(3-hydroxypropyl)-4-(2-methylpropyl)amino-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride hemihydrate; and (-)-trans-5,6-dihydro-6-(3-methoxy)propyl-4-propylamino-4H-thieno-[2,3-b]thiopyran-2-sulfonamide 7,7-dioxide.

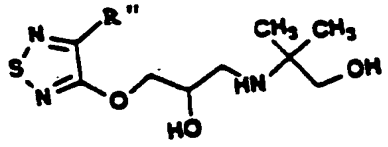
28. The composition of claim 27, wherein the carbonic anhydrase inhibitor is selected from the group consisting of: (R)-3,4-Dihydro-4-ethylamino-2-(3-methoxy)propyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride and (R)-3,4-Dihydro-4-ethylamino-2-(2-methoxy)ethyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride; (R)-4-ethylamino-3,4-dihydro-2-(4-

methoxy)butyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide; (R)-3,4-dihydro-2-(4-methoxy)butyl-4-propylamino-2-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide; (-)-trans-5,6-dihydro-6-(3-methoxy)propyl-4-propylamino-4H-thieno-[2,3-b]thiopyran-2-sulfonamide 7,7-dioxide.

29. The method of claim 24, wherein the beta-blocker is selected from the racemic and enantiomeric forms of: betaxolol, timolol, metoprolol, befunolol, falintolol, levobunolol, carteolol, mepindolol, pindolol, bisoprolol, bopindolol, atenolol, arotinolol, acebutolol, nadolol, celiprolol, metipranolol, bevantolol, ICI 118,551, pamatolol, penbutolol, toliprolol, tiprenolol, practolol, procinolol, exaprolol, cicloprolol, carazolol, tazolol, tienoxolol, oxprenolol, propranolol, IPS 339, labetolol, dilevalol, esmolol, bupranolol, bunolol, isoxaprolol, diacetolol and hydroxylevobunolol, and their pharmaceutically acceptable salts.

30. The method of claim 29, wherein the beta-blocker is selected from the group consisting of: betaxolol, timolol, carteolol, levobunolol and hydroxylevobunolol, and their pharmaceutically acceptable salts.

31. The method of claim 24, wherein the beta-blocker is a thiadiazole of formula:



(II)

and optically active isomers and pharmacologically acceptable salts thereof, wherein R" is selected from the group consisting of: hydrogen, halogen, C_{1-5} alkyl, C_{2-5} mono-alkenyl, C_{2-5} alkoxy, C_{3-6} cycloalkyl, phenyl, phenalkyl, morpholino, furyl, thienyl and pyrryl.

32. The method of claim 31, wherein R" is selected from the group consisting of: chlorine, ethyl, allyl, cyclopropyl, ethoxy, phenyl, phenyl-chloromethyl and 2-(cyclopropylmethoxy)ethyl.